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The Synthesis and Larvicidal Activity of *N*-Aroyl-*N′*-(5-aryl-2-furoyl)ureas

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Abstract: A novel type of diarolyurea compound containing a furan ring has been designed and prepared. Thus, a series of *N*-aroyl-*N′*-(5-aryl-2-furoyl)ureas were synthesized by a nucleophilic addition reaction between 5-substituted furamide and aroyl isocyanate in high yield (>80%). Their structures were confirmed by IR, [^{1}H]NMR and elemental analyses. Bioassay showed that some of them exhibited activity against second-instar larvae of the yellow fever mosquito (*Aedes aegypti* L.). With the aid of artificial neural network combined with multivariable regression, a preliminary study was made of structure–activity relationship. © 1998 SCI.

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Key words: diaroylurea; larvicidal activity; structure–activity relationship; *N*-aroyl-*N′*-(5-aryl-2-furoyl)ureas; yellow fever mosquito

1 INTRODUCTION

Chitin is the most abundant organic skeletal component in the cuticle of insects, but it is absent in vertebrates (including mammals) and higher plants. Thus, the development of selective insecticides based on interference with chitin formation has become one of the aims in new pesticide design.[1] Benzoylphenyl ureas, discovered in the 1970s, are well-known commercial chitin formation inhibitors, with excellent activity, low mammalian toxicity and good safety in the environment. The typical symptom of inhibited insects is the disruption of exuviation. In order to discover new selective insecticides, diaroylureas containing the furan ring **1** (Fig. 1) have been designed.

It is well known that the prosubstance (UDP-*N*-acetyl-glucosamine, UAGA) and chitin synthetase are targets for insecticide action in the process of chitin formation.[2] A structure possessing a peptide-like group (—NHCO—) which can form hydrogen bonds with peptides of proteins and enzymes in a biological body was regarded as likely to have enzyme-inhibiting properties.[3] The designed structure **1** not only contains a peptide-like group, but is also similar to UAGA. Therefore, it could be a chitin synthetase inhibitor or competitive inhibitor for UAGA and disrupt insect exuviation.

In this paper, we report the synthesis of 37 novel diaroylureas and their larvicidal activity against the yellow fever mosquito (*Aedes aegypti* L.). The bioassay demonstrated that some of them disrupt the moulting of mosquito larvae at 10 mg litre^{-1}. Preliminary QSAR was also carried out using CASAC software.

2 EXPERIMENTAL METHODS

2.1 Instruments and analysis

Melting points measured on Mel-Tem apparatus (Yanagimoto Mfg Co.) were uncorrected and are shown in Table 1. Infrared spectra were recorded on a Shimadzu spectrophotometer (IR-435, Japan) with potassium bromide pellets. Proton nuclear magnetic

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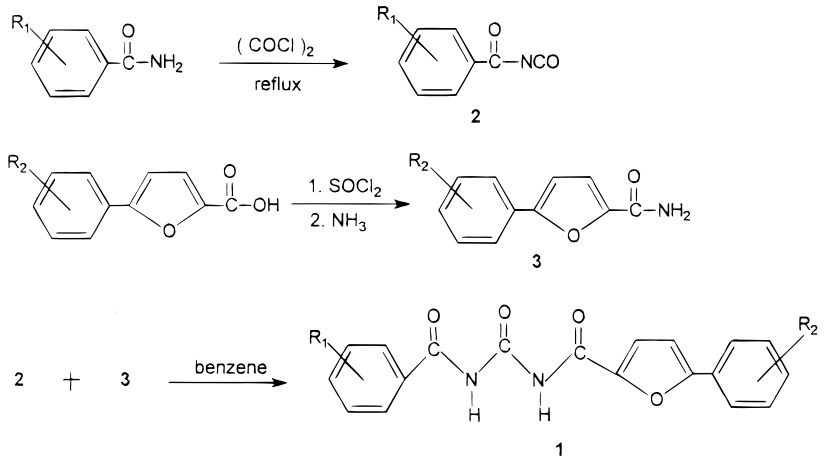

Fig. 1. Synthetic route to the novel diaroylurea.

resonance spectra were recorded on a JEOL (model FX-90 MHz) or VARIAN (model Unity-200 MHz) NMR spectrometer using deuterodimethyl sulfoxide as the solvent. Chemical shifts were given in parts per million relative to tetramethylsilane as internal standard. Elemental analyses were performed at the laboratories of the Institute of Chemistry, Chinese Academy of Sciences. The analytical values for C, H and N agreed with calculated values within $\pm 0{\cdot}3\%$.

2.2 Chemical synthesis

The general route to the product is depicted in Fig. 1. All the new diaroylureas synthesized are presented in Table 1. Typical synthetic procedures are exemplified as follows.

2.2.1 General procedure for substituted benzoyl isocyanate 2[4]

A mixture of benzamide (0·05 mol) and dry ethylene dichloride (50 ml) was stirred while oxalyl chloride (0·10 mol) was added rapidly. The mixture was stirred and refluxed till no further hydrogen chloride gas appeared. The ethylene dichloride was distilled off under vacuum and the aroyl isocyanate **2** was isolated as a colourless liquid by distillation under reduced pressure. Yields: 75–93%.

2.2.2 General procedure for 5-aryl-2-furamide 3

By the method of Krutosikova and Kovac,[5] a series of intermediate furamides were prepared. Thus, a mixture of 5-aryl-2-furancarboxylic acid (0·05 mol) and thionyl chloride (0·15 mol) was refluxed for 3 h. The excess of thionyl chloride was distilled off, and the residue was dissolved in benzene, to which ammonia was introduced at 5°C for 30 min. The mixture was allowed to stand for 1 h at room temperature, and the separated ammonium chloride was filtered and washed with benzene. The combined benzene solution was washed successively with 5% hydrochloric acid, water, 5% sodium carbonate solution and again with water. After drying over anydrous sodium sulfate, the benzene was distilled off and the residue crystallized from ethanol. Yields: 60–94%.

2.2.3 General procedure for diaroylurea

A mixture of an isocyanate (0·0015 mol), anhydrous benzene (10 ml) and a furamide (0·0015 mol) was stirred and refluxed for 3 h. After cooling, the resulting precipitate was collected and washed with benzene. On crystallization from dimethyl formamide + water (3 + 1 by volume), the target diaroylurea was obtained in good yield. For the representative compound **1t**, yield: 83·5%. m.p. = 189–191°C; elemental analysis calcd for $C_{20}H_{15}ClN_2O_4$: C, 62·75; H, 3·95; N, 7·32; found: C, 62·64; H, 4·10; N, 7·42. IR (ν_{max}, cm^{-1}) 3260(N—H), 2980(C—H), 1770(C=O), 1673(C=O). [^{1}H]NMR (δ, Unity-200 MHz): 12.80(NH), 11·72(NH), 8·10–7·25(m, 10H, BenH + FuH), 2·42(s, 3H, CH_3).

2.3 Biological assay

Dechlorinated tap water (200 ml) in a glass cup containing 10 mg $litre^{-1}$ of diaroylurea was supplied with 25 second-instar larvae of yellow fever mosquito (*Aedes aegypti* L.) and kept at 25°C. After 72 h, the mortality percentages were calculated with a correction for the natural mortality.[6] Chlorfluazuron was used for comparison. All the experiments were carried out in triplicate and the results, as mean values, are given in Table 1.

In the meantime, the activity against adult mosquitoes (*Culicidae*, at 2 mg $litre^{-1}$), oriental armyworm (*Leucania separata* Walker, at 200 mg $litre^{-1}$), cowpea aphid (*Aphis coaccivora* Koch, at 200 mg $litre^{-1}$), confused flour beetle (*Tribolium confusum* Jacquelin et Val, at 50 mg $litre^{-1}$), carmine spider mite (*Tetranychus cinnabarinus* (Boisd.) at 200 mg $litre^{-1}$) and European corn borer (*Ostrinia nubilalis* (Hübn) at 500 mg $litre^{-1}$) has been studied by immersion method or residual film method. These preliminary screening tests were carried

TABLE 1
Structure and Larvicidal Activity (Found and Calculated) of Diaroylureas

No.	b_2	b_3	b_4	f_2	f_3	f_4	*m.p* (°C)	*A*	*log* A_{test}	*log* A_{ANN}[a]	Δ *log* A[b]
1a	H	H	H	H	H	H	209–211	92	1·96	1·72	0·24
1b	H	H	H	Cl	H	H	185–187	40	1·60	1·73	−0·13
1c	H	H	H	H	H	Cl	186–187	36	1·56	1·53	0·03
1d	H	H	H	NO_2	H	H	177–179	8	0·90	0·85	0·05
1e	H	H	H	H	NO_2	H	199–201	48	1·68	1·72	−0·04
1f	H	H	H	H	H	NO_2	192–194	40	1·60	1·48	0·12
1g	H	H	H	H	H	OCH_3	191–193	16	1·20	1·51	−0·30
1h	H	H	H	H	Cl	Cl	207–209	68	1·83	1·53	0·30
1i	Cl	H	H	H	H	H	167–169	0	0·00	0·05	−0·05
1j	Cl	H	H	H	H	Cl	183–185	0	0·00	0·41	−0·41
1k	Cl	H	H	NO_2	H	H	175–178	12	1·08	1·07	0·01
1l	Cl	H	H	H	H	NO_2	178–180	36	1·56	1·42	0·13
1m	Cl	H	H	H	H	OCH_3	166–168	16	1·20	0·97	0·23
1n	H	Cl	H	H	H	F	190–192	48	1·68	1·61	0·07
1o	H	Cl	H	H	Cl	Cl	209–211	24	1·38	1·41	−0·03
1p	CH_3	H	H	H	Cl	H	200–202	12	1·08	1·36	−0·28
1q	CH_3	H	H	H	H	F	211–212	80	1·90	1·89	0·01
1r	CH_3	H	H	H	NO_2	H	215–217	52	1·72	1·36	0·35
1s	H	CH_3	H	H	H	H	190–192	24	1·38	1·41	−0·03
1t	H	CH_3	H	H	H	Cl	189–191	20	1·30	1·33	−0·03
1u	H	CH_3	H	NO_2	H	H	182–184	4	0·60	0·65	−0·05
1v	H	CH_3	H	H	NO_2	H	198–199	28	1·45	1·42	0·03
1w	H	CH_3	H	H	H	OCH_3	184–186	20	1·30	1·30	0·00
1x	H	H	CH_3	H	Cl	H	189–191	20	1·30	1·55	−0·25
1y	H	H	CH_3	H	NO_2	H	187–189	80	1·90	1·55	0·35
1z	F	H	H	H	H	H	180–182	40	1·60	1·68	−0·08
1aa	F	H	H	H	H	Cl	178–180	20	1·30	1·52	−0·22
1bb	H	H	Br	H	H	H	212–213	8	0·90	0·88	0·02
1cc	H	H	Br	H	H	Cl	219–221	36	1·56	1·70	−0·14
1dd	H	H	Br	NO_2	H	H	179–181	12	1·08	1·08	−0·00
1ee	H	H	Br	H	H	OCH_3	200–202	36	1·56	1·68	0·12
1ff	Cl	H	Cl	H	H	H	180–182	80	1·90	1·58	−0·32
1gg	Cl	H	Cl	Cl	H	H	196–198	20	1·30	1·31	−0·01
1hh	Cl	H	Cl	H	H	Cl	200–202	24	1·38	1·46	−0·08
1ii	Cl	H	Cl	H	H	F	198–200	20	1·30	1·39	−0·09
1jj	Cl	H	Cl	NO_2	H	H	186–188	0	0·00	0·03	−0·03
1kk	Cl	H	Cl	H	H	OCH_3	203–205	16	1·20	1·44	−0·23

[a] ANN: recorrelation coefficient ($r = 0{\cdot}95$), standard deviation ($s = 0{\cdot}18$).
[b] $\Delta\log A = \log A_{test} - \log A_{ANN}$. Activity (A) of Chlorfluazuron: 100%.

out by the Bioassay Laboratory of Institute of Elemento-Organic Chemistry (NanKai University, Tianjin, China). Three replicates were used per treatment. Each replicate consisted of 20 adult pests (for oriental armyworm and carmine spider mite 50 adult pests respectively). None of the novel compounds showed any activity in these tests.

2.4 Preliminary study on structure–activity relationship

Software: CASAC[7] (Computer-Aided Screening bio-Active Compounds), made by Laboratory of Computer Chemistry (LCC), Institue of Chemical Metallurgy, Chinese Academy of Sciences, Beijing, China.

Method: With improved artificial neural network (ANN) combined with multiple linear regression (MLR) in this software, ANN and MLR are complementary in the calculation.[8,9]

Physicochemical parameters: All parameters in the model are generated by means of both the parameter database and structural matching module in CASAC Software. They are shown in Table 2.

Structural frame model (*SFM*) *of diaroylurea*: The SFM of diaroylurea was obtained by forming in CASAC (Fig. 2).

The following equation obtained by MLR is unsatisfied, but the variables (Table 3) are independent of each

TABLE 2
Values of Parameters Used[a]

	DP	*EN*	L_1	B_5
H	0·00	2·30	2·06	1·00
Cl	0·95	3·10	3·52	1·80
CH_3	0·26	2·47	3·00	2·04
Br	1·18	2·87	3·53	1·95
NO_2	4·94	3·63	3·44	2·44
OCH_3	1·14	3·46	3·48	2·87

[a] DP: dipole moment, EN: electronegativity, L_1: length, B_5 breadth.

other. This indicated that there may be a mainly non-linear relationship between structure and activity.

$$\log A = -0{\cdot}12(\pm 0{\cdot}09)DP[f_2] - 0{\cdot}32(\pm 0{\cdot}25)L_1[b_2] - 0{\cdot}20(\pm 0{\cdot}42)B_5[b_3] + 0{\cdot}05(\pm 0{\cdot}13)DP[f_4] + 0{\cdot}13(\pm 0{\cdot}42)EN[b_4] + 2{\cdot}12(\pm 0{\cdot}89)$$

$$n = 37 \quad s = 0{\cdot}43 \quad r = 0{\cdot}60 \quad F = 3{\cdot}41$$

Taking the five important variables selected by MLR as the input parameters in the ANN programme, whose net model is [5-3-1] (consisting of five input nodes, three hidden nodes and one output node), and the condition of learning rate = 0·10, correct factor = 1·01 and momentum factor = 0·60, the values shown in Table 1 were obtained.

3 RESULTS AND DISCUSSION

The preliminary bioassay indicated that some of the diaroylureas show larvicidal activity against *A. aegypti* at 10 mg litre^{-1} with the same lethal effects as chlorfluazuron, but have no activity on adult insects. Among them, compounds **1a**, **1q**, **1y** and **1ff** show the highest

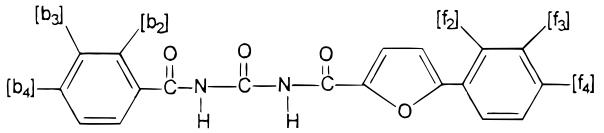

Fig. 2. SFM of diaroylurea group in square brackets ([ ]) is variable.

TABLE 3
Correlation Coefficient of Variables

	$DP[f_2]$	$L_1[b_2]$	$EN[b_4]$	$DP[f_4]$	$B_5[b_3]$
$L_1[b_2]$	0·03				
$EN[b_4]$	0·11	0·39			
$DP[f_4]$	−0·28	0·09	−0·11		
$B_5[b_3]$	0·01	−0·39	−0·30	−0·06	
log A	−0·45	−0·34	−0·10	0·19	−0·02

mortality to larvae, but none is more active than chlorfluazuron.

The results of preliminary MLR show that there is no evident linear relationship between physicochemical parameters and activity (log A). Therefore, artificial neural network (ANN) method was also introduced. ANN is valuable for dealing with non-linear relationships between structure and activity, but has two disadvantages. First is the difficulty of explaining the network information. The second one is the overfitting phenomenon. The CASAC software solves the second problem with its improved ANN method,[8] while the first problem can be solved by combination with the MLR method. In other words, the MLR supports ANN with a rational explanation when the input parameters of ANN are those selected by MLR. Thus, taking the five important variables selected by MLR as the input parameters for ANN, we obtained a more accurate model for predicting active compounds than with the MLR method alone, with the standard deviation reduced from 0·43 to 0·18. Furthermore, the increasing value (from 0·6 to 0·93) of the recorrelation coefficient proved that there is really a non-linear relationship between selected parameters and activity. According to the results of both ANN and MLR, dipole moment, f_2, the length, b_2, and the breadth, b_3, are important factors affecting the activity. This result will be very useful for the next designing step.

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